

Claims 1 and 4-6 were finally rejected under 35 U.S.C. 103 as being unpatentable over Schmidt-Ruppin et al. for the reasons set forth in the prior Action. Therein, it was contended that said reference teaches "the use of topical creams and ointments containing zinc oxide . . . which may additionally contain biologically active substances including Miconazole . . . The determination of both optimum proportions and target use are matters of obvious alternative to one with skill in the art".

As previously stated, the Schmidt-Ruppin et al. reference discloses a method of treating herpes infections by administering anthracene-type compounds and compositions containing same. These anthracene compounds act upon the central nervous system, and it is alleged thereby combat herpes infections. In column 7, line 43 of the reference, it indicates that pharmaceutical preparations containing these anthracene actives for topical use can be in the form of creams, ointments, gels, vaginal ovula, pastes, foams, tinctures and solutions; and in column 8, line 30 et seq., it further indicates that pastes are creams and ointments having secretion absorbing powder constituents such as metal oxides, including zinc oxide. It also states that biologically active substances including miconazole can be added to these compositions.

Applicants respectfully contend that the teachings and disclosures of the Schmidt-Ruppin et al. reference would neither teach nor suggest to one skilled in the art the present invention. To contend that from the teaching of utilizing anthracene-type actives to act upon the central nervous system one skilled in the art would arrive at the present invention is

not reasonable. To obtain Applicants' compositions from this reference, one would have to formulate the composition containing the anthracene compound in a cream form utilizing zinc oxide and add thereto miconazole and then delete the anthracene active and adjust the ratios of the remaining components. Such is clearly not obvious from the teachings of Schmidt-Ruppin et al.

The compositions of the present invention are limited to skin care compositions containing miconazole nitrate and zinc oxide in specific ratios which exhibit synergistic interaction. There is no intent whatsoever of including systemically active compounds such as the anthracene compounds disclosed in the reference, and the Examiner's reliance on this reference is considered inappropriate in view of the teachings therein.

Support for Applicants' claimed compositions with specific ratios of miconazole nitrate to zinc oxide can be found in the specification and examples. Table I on page 12 of the specification shows synergistic activity for ratios of miconazole nitrate to zinc oxide against Staphylococcus aureus of 1:110 to 1:333 and above. In Table II, synergistic activity is shown for ratios of about 1:40 to 1:333 and above. No additional data was deemed necessary to be collected for ratios above about 1:333 since 100% inhibition is recorded. Any differences found in the results recorded in these two tables are within the normal experimental fluctuation that one finds in two-fold serial dilution experiments.

Table III on page 14 of the specification shows synergistic activities for ratios of miconazole nitrate to zinc oxide against Candida albicans of 1:240 and above and Table IV

on page 15 shows synergistic activity for ratios of miconazole nitrate to zinc oxide against Candida albicans of 1:120 and above. Once again, any variations in the data reported in these two tables are within the normal experimental fluctuation that one finds in two-fold serial dilution experiments.

Synergistic efficacy of the combinations of miconazole nitrate to zinc oxide in a ratio of 1:60 against Candida albicans are shown in Example VI on pages 9 and 10 of the specification. This is a recognized in vivo test procedure and involves both microbiological measurements and clinical measurements. This procedure results in microbiological measurements from the cultures obtained by a standard detergent scrub method and clinical measurements taken by observations at various time periods. The results of these testing procedures show a statistically significant synergistic effect for the combination of miconazole nitrate and zinc oxide in a ratio of about 1:60 against Candida albicans.

This in vivo procedure was explained in more detail in the Declarations Under Rule 132 of Dr. Bruce Semple and Dr. James J. Leyden submitted with the Amendment dated March 18, 1986. Dr. Semple, who is Vice-President - Scientific Affairs, Johnson & Johnson Baby Products, authorized this test procedure to be conducted at the Ivy Research Laboratories under the direction of Dr. Leyden.

In the present Office Action, it is contended that "The Declaration of Semple regarding Candida Albicans is not persuasive as it fails to present the data from which its conclusions were derived". During the aforementioned interview, the Examiners suggested that this data should be in a more "visible" format.

Applicants are therefore submitting herewith a further Declaration of Dr. Bruce Semple. In this Declaration, the microbiological results are again discussed and summarized and are also represented in tabular form on page 4. The results very clearly and visibly demonstrate the claimed synergism. This synergism, as summarized in the table in said Declaration, is demonstrated beyond the possibility of mere experimental error due to the exactness of the microbiological counts and the statistical model utilized which has a p factor of $p < 0.05$.

In the Semple Declaration Under Rule 132, the clinical aspects of Dr. Leyden's work are again set forth and summarized and are further represented in graphical format. Applicants respectfully contend that these clinical results clearly demonstrate the synergistic nature of the compositions of the present invention.

In the present Office Action, it was indicated that the data submitted in the Isaacson Declaration Under Rule 132 was convincing but some question is raised as to the seemingly different data obtained at a second reported concentration for the miconazole nitrate activity. This is due to the experiment variation often found in test procedures of this nature and particularly when low concentrations are utilized. The important thing to note is that synergism was clearly demonstrated at both concentrations against Staphylococcus aureus in a ratio of 1:60 of miconazole nitrate to zinc oxide.

It is respectfully contended that the claims presently in the application find adequate support in the specification and find additional adequate experimental support in the Declaration Under Rule 132 submitted herewith as well as the previously submitted Declarations under Rule 132. Accordingly,